1-Pyrrolidinomethyl-4-pyrrolidinomethylaminopyrazolo[3,4-d]pyrimidine (V). This compound, with mp 105-106°C (from petroleum ether), was obtained in 40% yield by a method similar to that used to prepare III. Found: C 59.7; H 7.7; N 32.5%. $C_{15}H_{23}N_7$. Calculated: C 59.8; H 7.7; N 32.5%.

1-Methyl-4-(N-methylpiperazinomethyl)aminopyrazolo[3,4-d]pyrimidine (VI). This compound, with mp 205-206°C (reprecipitation from ethyl acetate by the addition of hexane), was obtained in 60% yield by a method similar to that used to prepare III. Found: C 58.6; H 7.5; N 33.9%. $C_{12}H_{19}N_7$. Calculated: C 58.5; H 7.3; N 34.1%. UV spectrum, λ_{max} (ε), pH 10.9; 265 nm (11,600).

4-Bromopyrazolo[3,4-d]pyrimidine (VIIa). A suspension of 0.3 g (2.2 mmole) of 4-hydroxypyrazolo[3,4-d]pyrimidine in 8 ml of hydrobromic acid (sp. gr. 1.5) was cooled to 0-5°C, and 0.8 g (5 mmole) of bromine and 0.4 ml of a 10% solution of sodium nitrite were added. The mixture was stirred at 0°C for 2 h and allowed to stand in a refrigerator overnight. Workup gave 0.3 g (40%) of VII with mp 280-281°C (dec., from benzene). PMR spectrum: 8.26 (3H, s) and 8.29 ppm (6H, s). Found: Br 39.8; N 28.0%. $C_5H_3BrN_4$. Calculated: Br. 40.1; N 28.1%.

4-Bromo-1-methylpyrazolo[3,4-d]pyrimidine (VIIb). This compound, with mp 253-254°C (from benzene), was obtained in 40% yield by a method similar to that used to prepare VIIa. PMR spectrum (in $CDCl_3$): 3.97 ($1CH_3$, s) and 8.28 ppm (3, 6H, s).

LITERATURE CITED

1. T. S. Leonova, T. A. Babushkina, and V. G. Yashunskii, Khim. Geterotsikl. Soedin., No. 10, 1414 (1973).
2. T. S. Leonova, T. A. Babushkina, and V. G. Yashunskii, Khim. Geterotsikl. Soedin., No. 3, 397 (1978).
3. P. Smidt, K. Eihenberger, M. Wilhelm, and J. Dryey, Helv. Chim. Acta, 42, 763 (1979).
4. E. G. Tauior and Achmad Abdul-Husn, J. Org. Chem., 31, 342 (1966).

MOLECULAR-CRYSTAL STRUCTURE OF 5-METHYL-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-2-ONE

S. A. Andronati, A. A. Dvorkin, T. I. Korotenko, T. A. Voronina, Yu. A. Simonov, and T. A. Shibanova

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5-Methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one, which is an antagonist of 5-aryl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones, was subjected to a complete x-ray diffraction study. The crystals have monoclinic syngony with a = 11.456(5), b = 8.195(3), c = 9.257(4) Å, γ = 93.10(3)°, and space group $P2_1/b$. The nonplanar molecules (with a boat conformation) form cyclic dimers by means of NH...O hydrogen bonds (2.937 Å) in the vicinity of the center of symmetry (0, 0, 1/2). Replacement of the phenyl ring in the 5 position by a less bulky methyl group does not lead to appreciable changes in the geometry and conformation of the heteroring. It is assumed that the substituent in the 5 position plays a role in determining the character of the pharmacological action of 1,4-benzodiazepines.

A study of the dependence of the IR spectra of solutions of 1-unsubstituted 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones in carbon tetrachloride on the temperature showed that the molecules of these compounds in a nonpolar solvent are associated due to hydrogen bonds between the amide groups, thereby forming, depending on the concentration, linear intermolecular associates Ia or cyclic dimers Ib [1].

Physicochemical Institute, Academy of Sciences of the Ukrainian SSR, Odessa 270080. Institute of Applied Physics, Academy of Sciences of the Moldavian SSR, Kishinev 277028.

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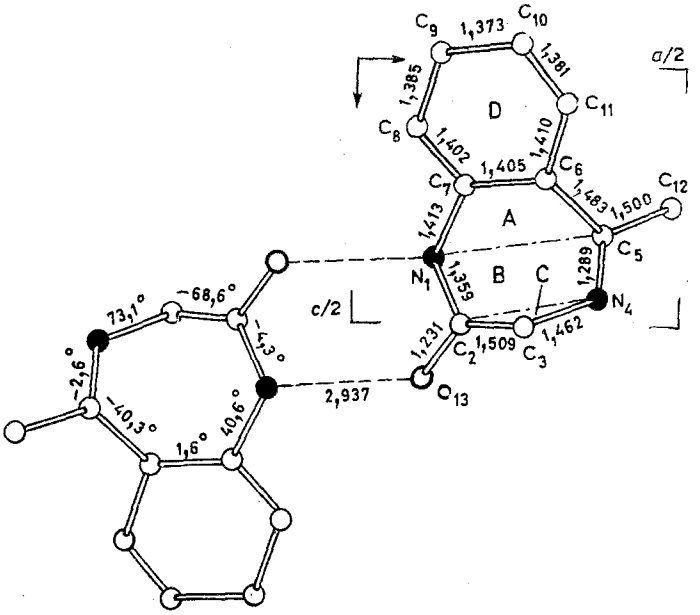
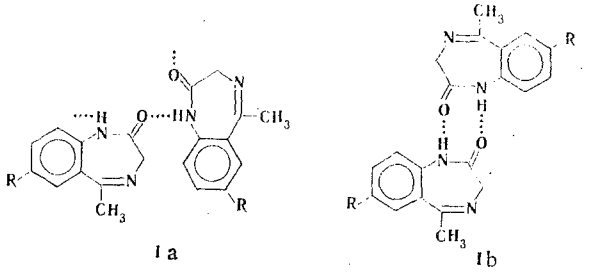


Fig. 1. Cyclic dimer of 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one in projection on the xz plane. The torsion angles in the heteroring are presented in the left-hand molecule, and the interatomic distances are presented in the right-hand molecule.



Ia Ib

It has been shown by spectral methods [2] that the heteroring of 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones has a boat conformation and that inversion of two equivalent conformations occurs in solutions. These data regarding the structure and inversion of 5-methyl-1,4-benzodiazepines constitute evidence for an analogy between them and 5-aryl-1,4-benzodiazepines, although they cannot explain the data on the pharmacological activity of 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one, which differ substantially from the activity of the 5-aryl analogs. It is known that in the organisms 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one is an antagonist of 5-aryl,1,4-benzodiazepines and displays convulsant properties [3].

In order to ascertain the peculiarities of the structure of I that may determine the character of their pharmacological action we undertook a complete x-ray diffraction investigation of 5-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (II).

A dimeric fragment of the structure in projection on the xz plane is presented in Fig. 1. The molecule is a nonplanar seven-membered heteroring conjugated with the benzene ring. The principal distances are presented in Fig. 1, while the bond angles are presented in Table 1. The errors in the distances range from 0.002 to 0.003 Å, while the error in the angles is 0.2°. If one compares the distances in II with the distances in diazepam [4], the principal geometric parameters of the molecules coincide within the limits of the standard deviations. The N_1—C_7 distance of 1.413 Å is somewhat shorter than in diazepam (1.422 Å), while the C=O distance of 1.231 Å is appreciably greater than in diazepam (1.218 Å). If one compares the bond angles, the C_7—N_1—C_2 angle of 126.4° differs substantially: it is almost 3° greater than the corresponding angle in diazepam, which is evidently explained by replacement of the methyl group in this position by a hydrogen atom. This is also observed in other similar compounds with a hydrogen atom in the 1 position [5, 6]. The environment of the N_1 atom is planar, and

TABLE 1. Bond Angles in the Molecules of Dimer II

Angle	Value, deg	Angle	Value, deg
$C_7—N_1—C_2$	126,4	$C_{12}—C_5—C_6$	117,1
$N_1—C_2—C_3$	115,2	$C_5—C_6—C_{11}$	119,5
$C_2—C_3—N_4$	111,3	$C_{11}—C_6—C_7$	117,9
$C_3—N_4—C_5$	117,2	$C_6—C_7—C_8$	119,7
$N_4—C_5—C_6$	125,5	$N_1—C_7—C_8$	116,8
$C_5—C_6—C_7$	122,4	$C_7—C_8—C_9$	120,6
$C_6—C_7—N_1$	123,3	$C_8—C_9—C_{10}$	120,2
$N_1—C_2—O_2$	121,7	$C_9—C_{10}—C_{11}$	120,0
$O_2—C_2—C_3$	123,2	$C_{10}—C_{11}—C_6$	
$N_4—C_5—C_{12}$	117,4		

TABLE 2. Coordinates of the Nonhydrogen ($\cdot 10^4$) and Hydrogen ($\cdot 10^3$) Atoms (with the standard deviation in parentheses)

Atom	x	y	z	Atom	x	y	z
N_1	1229 (2)	779 (2)	3774 (2)	O_{13}	1103 (1)	907 (3)	6210 (1)
C_2	1594 (2)	1356 (3)	5084 (2)	H_1	52 (3)	13 (4)	372 (3)
C_2	2626 (2)	2580 (3)	5046 (2)	H_{31}	272 (2)	310 (3)	605 (2)
N_4	3692 (2)	1814 (2)	4600 (2)	H_{32}	244 (1)	351 (2)	450 (2)
C_5	3778 (2)	1423 (2)	3257 (2)	H_8	7 (2)	116 (3)	152 (3)
C_6	2869 (2)	1623 (2)	2140 (2)	H_9	59 (3)	187 (4)	−81 (4)
C_7	1673 (2)	1290 (2)	2413 (2)	H_{10}	266 (3)	241 (4)	−141 (3)
C_8	866 (2)	1350 (3)	1279 (2)	H_{11}	400 (3)	223 (3)	54 (3)
C_9	1234 (2)	1764 (3)	−105 (2)	H_{121}	477 (3)	−19 (5)	208 (5)
C_{10}	2397 (2)	2137 (3)	−378 (2)	H_{122}	541 (4)	51 (6)	363 (6)
C_{11}	3207 (2)	2052 (3)	719 (2)	H_{123}	540 (4)	149 (6)	219 (5)
C_{12}	4899 (2)	730 (3)	2774 (3)				

the sum of the angles at it is 359.4°. As in the case of other 1,4-benzodiazepines, the heteroring has a boat conformation. The $N_1—C_5—C_6—C_7$ (A), $N_1—C_2—N_4—C_5$ (B), and $C_2—C_3—N_4$ (C) fragments are planar: the maximum deviations of the atoms from the average plane are, respectively, ±0.007, ±0.012, and 0 Å. The dihedral angles are as follows: A, B 32.5°; B, C 120.2°; A, C 87.8°. The conjugated benzene ring (D) is virtually planar (the deviation of the atoms is ±0.011 Å) and forms an angle of 4.5° with the Å plane.

The amide fragments of diazepinone II molecules participate in the formation of an NH...O intermolecular hydrogen bond (2.937 Å), which links the individual molecules together to form cyclic dimers in the vicinity of the center of symmetry (0, 0, 1/2).

Thus replacement of the bulky phenyl substituent in the 5 position by a methyl group does not lead to an appreciable change in the conformation and geometry of the heterocyclic part. This makes it possible to assume that the phenyl substituent in the 5 position plays a fundamental role in determining the pharmacological properties of benzodiazepines.

It may be assumed that the presence of an aryl substituent in the 5 position in 1,4-benzodiazepines ensures complementary character of the benzodiazepine tranquilizer molecules with respect to the sites of their specific bonding in the central nervous system [7].

EXPERIMENTAL

5-Methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one was synthesized by the method in [2]. A single crystal with a lamellar habitus and dimensions 0.3 mm by 0.4 mm by 0.8 mm was selected for x-ray diffraction study.

The crystals have monoclinic syngony with unit cell parameters a = 11.456(5), b = 8.195-(3), c = 9.257(3) Å, and γ = 93.10(3)°. The calculated density (ρ) was 1.333 g/cm^3 for Z = $4 \cdot C_{10}N_2OH_{10}$. The space group was $P2_1/b$.

The experimental data were obtained with a DAR-UMBK automatic equiinclination diffractometer [Mo K_α° graphite monochromator, ω–$\theta/2\theta$ method, $(\sin\theta/\lambda)_{max}$ = 0.6 Å^{-1}] and consisted of 1287 reflections with $I \geqslant 3\sigma$. The L_p factor was taken into account in scaling of F^2. The absorption and extinction were not taken into account.

The structure was solved by direct methods. Several stages of the method of least squares within the anisotropic approximation in the total-matrix variant by means of the YANX program (A. N. Nesmeyanov Institute of Heteroorganic Compounds of the Academy of Sciences of the USSR, adapted for an ES computer) led to R = 0.089. All of the hydrogen atoms were localized confidently by differential synthesis. Three stages of the method of least squares with refinement of the position of the hydrogen atoms within the isotropic approximation decreased R to 0.057. The final coordinates of the basis atoms of the structure are presented in Table 2.

LITERATURE CITED

1. S. A. Andronati, I. E. Boldeskul, T. I. Korotenko, I. F. Tsymbal, and L. N. Yakubovskaya, Summaries of the Papers Presented at the 13th Ukrainian Republican Conference on Physical Chemistry, Odessa (1980), p. 295.
2. A. V. Bogat-skii, S. A. Andronati, V. I. Minkin, L. E. Nivorozhkin, V. S. Yur'eva, and T. I. Korotenko, Problems in Stereochemistry [in Russian], Vol. 7, Odessa–Kiev (1978), p. 3.
3. W. Schlosser and S. Franco, J. Pharmacol. Exp. Ther., No. 2, 290 (1979).
4. A. Camerman and N. Camerman, J. Am. Chem. Soc., 94, 268 (1972).
5. A. A. Karapetyan, V. G. Andrianov, Yu. T. Struchkov, A. V. Bogat-skii, S. A. Andronati, and T. I. Korotenko, Bioorg. Khim., 5, 1684 (1979).
6. G. Gilly, V. Bertolasi, M. Sacerdoti, and P. A. Borea, Acta Crystallogr., B33, 2664 (1977).
7. L. F. Tallman, S. M. Paul, P. Skolnick, and D. N. Gallager, Science, 207, 274 (1980).

SYNTHESIS AND IDENTIFICATION OF ESTERS OF ISOMERIC TETRAHYDROPYRANYL-SUBSTITUTED 1-ARYLTRIAZOLECARBOXYLIC ACIDS

R. S. Vartanyan, Zh. V. Kazaryan,
R. G. Mirzoyan, and L. A. Gevorkyan

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541.621.2:543.422

The reaction of (2,2-dimethyltetrahydropyran-4-yl)propiolic acid esters with p-fluorophenyl azide leads to esters of isomeric tetrahydropyranyl-substituted 1-aryltriazolecarboxylic acids, which were identified by means of conversion to disubstituted triazoles; their structures were proved by physicochemical methods.

In order to create previously unknown biheterocyclic systems — tetrahydropyran derivatives — we synthesized β-(2,2-dimethyltetrahydropyran-4-yl)-β-oxopropionic acid and (2,2-dimethyltetrahydropyran-4-yl)propiolic acid esters [1, 2] as the starting compounds. When we used the latter as dipolarophiles in cyclization with p-fluorophenyl azide, we obtained mixtures of isomeric 1-(p-fluorophenyl)-4-(2,2-dimethyltetrahydropyran-4-yl)-5-carbethoxy- and 1-(p-fluorophenyl)-4-carbethoxy-5-(2,2-dimethyltetrahydropyran-4-yl)triazoles, which were separated by fractional crystallization.

In order to ascertain the spectral characteristics that would make it possible to identify the isomers, we hydrolyzed esters Ia, b to the corresponding acids IIa, b, and the latter were then decarboxylated to isomeric disubstituted triazoles VIIIa, b, which can be readily identified on the basis of known criteria [3, 4].

It is known that in triazoles and some other azoles the proton adjacent to the substituted nitrogen atom is more sensitive to the effects of the solvent [5]. It is also known that when both isomers are present, the resonance signals of the 5-H proton are observed at weaker field than the 4-H signals in both solvents in the PMR spectra recorded in deuterochloroform and dimethyl sulfoxide (DMSO). A large $\Delta\delta = \delta_{DMSO} - \delta_{CDCl_3}$ difference is characteristic for 1,4-

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan 375014.

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